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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,988	LEONARD ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,10-12,18,20 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 8, 10-12, 18, 20 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 5, 8, 10-12, 18, 20 and 32-35 are pending. Claims 5, 18, 34 and 35 have been amended by Applicant's amendment filed on 06-26-2008.
3. Therefore, claims 5, 8, 10-12, 18, 20 and 32-35 are currently under examination to which the following grounds of rejection are applicable.

Objections/rejections withdrawn in response to Applicant arguments or amendments:

Specification

In view of Applicant's arguments alleging that a statement reciting that the information recorded in computer readable form is identical to the written sequence listing is not necessary because Applicant only submitted a computer readable form to identify the amino acid sequence "WSXWS" as SEQ ID NO:17 on February 28, 2008 and not a written sequence listing, and further because the CRF of the replacement sequence listing is identical to the originally filed sequence listing (submitted in written form) except for the identification of SEQ ID NO: 17, objection to the specification has been withdrawn.

Claim objection

In view of Applicants appropriate renumbering of claims 32 and 33 to claims 34 and 35 after claims 32 and 33, objection to the claims has been withdrawn.

Objections/rejections maintained in response to Applicant arguments or amendments:

Claims 5, 8, 10-12, 18, 20 and 32-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Response to Applicant Arguments as they apply to rejection of Claims 5, 8, 10-12, 18, 20 and 32-35 under 35 USC § 112 - written description.

At page 6 of remarks, Applicants argue that the pending claims, drawn to IL-21 polypeptide or variants thereof producing the same physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor are sufficiently described in the specification in relation to the correlation between the function and the structure of any variant of IL-21 or any variant of SEQ ID No. 1 that differ from SEQ ID No. 1 by 1-5 amino acids. Indeed, Applicants indicates enough support for said variants of IL-21 at "page 31, lines 1-26. In particular, the specification cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retaining the essential properties thereof. In particular, Ebner et al. discloses conserved regions of IL-21 polypeptide in Figures 1, 4, 6A- B, and 7, and Tables I-III. Furthermore, Ebner et al. discloses regions of identity between IL- 21 and other interleukins in Figures 3A-C". Such is not persuasive.

As stated in the previous office action, the instant claims are drawn to a genus of IL-21, a genus of IL-21 variants and a genus unidentified variants of SEQ ID No. 1 that differ from SEQ ID No. 1 by 1-5 amino acids wherein said variants need not to retain full or even partial activity. The specification does not disclose regions or domains of the protein that are essential to bind the IL-21 receptor resulting in the claimed physiological effects. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. Furthermore, there is not description of the claimed fragments of SEQ ID No. 1 binding to the IL-21 receptor and being functionally active in such full, clear, concise and exact terms so as to indicate that Applicant has possession of a genus of amino acid sequences which differs by one, two, three, four or five amino acids from the amino acid sequence of SEQ ID No.1 at the time of filing the present application. A search of "IL-21" in the protein database available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein, conducted on October 2, 2007 provided 95 possible IL-21 proteins and it is unclear to which one(s) the claims refer. Furthermore, US Publication No. 20030003545 referred to by Applicants, discloses one species of IL-21, i.e., the nucleotide sequence of SEQ ID No. 1 and the corresponding encoded amino acid sequence of SEQ ID No. 3 with the description of conserved domains (e.g., Fig. 1) and sequence identity with hIL-17, mIL-17, viral IL-17, IL-20 and others. In addition US Publication No. 20030003545 merely discloses at page 9, paragraph [0073], "one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function". It is unclear how the functional secretory function of SEQ ID No. 3 of US Publication No. 20030003545 relates to the instantly claimed binding domain of SEQ ID No. 1, or how modification of the N-terminus or C-terminus amino acid sequence of instantly claimed

SEQ ID No. 1 affect the functionality of the protein. There is not structure/function relationship taught at all for SEQ ID No. 1, much less for a genus of IL-21 and a genus of IL-21 variants for the written description requirement to be satisfied. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim Rejections - 35 USC § 112 –scope of enablement

To the extent that the claims read on *ex vivo* methods for enhancing an immune response in a subject (claims 5, 8, 10-12) or treating a subject with a condition in a subject (claims 18-20, 32-35) comprising a specific deficiency of at least one of memory B and plasma cells, the following rejection apply.

Claims 5, 8, 10-12, 18, 20 and 32-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for claims directed to an *ex vivo* method of enhancing an immune response to a viral antigen or treating a subject with a condition comprising a specific deficiency of at least one of memory B and plasma cells comprising isolating a population of cells from the subject comprising one or more of a mature B cell and a cell progenitor, contacting said population with IL-21 of SEQ ID No. 1 or agonists of SEQ ID No. 1, so as to induce differentiation of said B cells into a memory B cell and a plasma

cell, respectively, wherein the population is optionally contacted with an antigen, isolating said a memory B cell and a plasma cell and introducing said population into the subject.

Response to Applicant Arguments as they apply to rejection of Claims 5, 8, 10-12, 18, 20, 32-35 under 35 USC § 112 - scope of enablement.

At page 8 of Remarks, Applicants argue that the invention is "directed to a method of enhancing an immune response by administering one or more of a memory B cell and the plasma cell produced *ex vivo* to the subject. The claims do not preclude that the subject experiences a cell-mediated immune response against an antigen (e.g., viral antigen). Nor do the claims recite that one or more of a memory B cell and the plasma cell induces an immune response. Rather, the claims recite that the addition of the memory B cell and plasma cell enhances (i.e., improves) an immune response in a subject." In addition applicants allege that "Viruses can be extracellular in the course of infection. Therefore, viral antigens can be extracellular antigens against which an immune response in the form of antibodies (e.g., against antigens of the viral envelope) would be beneficial. Thus, the administration of one or more of a memory B cell and the plasma cell can serve to enhance an immune response (e.g., a cellular-mediated immune response against a viral antigen)"[emphasis added]. Such is not persuasive.

The enabling issues are whether the broadly claimed methods provide sufficient guidance for inducing an immune response against a viral infection comprising isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from said subject, contacting said cells with IL-21 so as to induce differentiation of said B cells into a memory B cell and a plasma cell, respectively, purifying or isolating said memory B cell and a plasma cell and introducing this population into the subject. Applicants have not provided any evidences

supporting how an immune response against a viral infection is effective merely **by a humoral response** e.g., a memory B cell and a plasma cell that are administered back to the subject after isolation, as viruses are intracellular pathogens and an effective response against intracellular viral pathogens involves processing and association of the viral antigen to be presented with the MHC Class I molecule on APC cell surface for activation of T cells to induce a cell-mediated immunity. As stated in the previous office action, viruses can be extracellular in the course of the infection, however, the presence of antibodies in serum (e.g., a memory B cell and a plasma cell) may be directed against irrelevant or non-critical viral antigens, or the viral infection may be of a type that is not controlled at all by antibodies such as the in the case of intracellular herpes viruses infections (see, Mims et al., Medical Microbiology, third edition, 2004, pp. 150-152). Though it is unclear how a subject can experience a cell-mediated immune response by virtue of administering at least one or more of a memory B cell and the plasma cell or how a humoral response would be beneficial against any viral antigen, as claimed. In contrast to applicants' arguments, the presence of viral antigens in serum against envelope viral proteins such antibodies against the HIV-1 envelope gp120 and gp41does not imply an immune protective response, as the simply binding of the antibody molecule to the microbial surface do not necessary blocks HIV-1 entry into the target cell. In fact most treatment of HIV-infected individuals requires an intact cell-mediated immunity response for effective defense (Mims et al., Medical Microbiology, third edition, 2004, pp. 429-431). Furthermore, the specification is silent about examples of an *ex vivo* method of treating a subject with a condition characterized by a deficiency of at least a memory B cells and a plasma cells. The specification as filed fails to provide particular guidance to resolve the known unpredictability in the art associated with

treatment of an immunocompromised subject. The quantity of experimentation required to practice the methods as claimed would require the *de novo* determination of effective target sites, modes of delivery, safe administration of at least a memory B cells and a plasma cells to target appropriate cells and/or tissues in an immunocompromised subject, and further whereby treatment effects are provided for the claimed condition. Since the specification fails to provide particular guidance for the treatment of an immunocompromised subject comprising administration of at least a memory B cell and a plasma cell and the art teaches that treatment of a B cell deficient subject is highly unpredictable as evidence in the treatment of an immunocompromised HIV-infected individuals requiring an intact cell-mediated immune response, it would require undue experimentation to practice the invention as presently claimed. Hence, the scope of the patent protection sought by the Applicant as defined by the claim fails to correlate with the scope of enabling disclosure set forth in the specification.

In so far as the claimed genus of IL-21, genus of IL-21 variants and genus of unidentified variants of SEQ ID No. 1 that differ from SEQ ID No. 1 by 1-5 amino acids maintaining the claimed functionality, Applicants allege that "The specification describes variants for use in the invention at, for example, page 31, lines 1-26, and cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retaining the essential properties thereof. Ebner et al. discloses conserved regions of IL- 21 polypeptide, such that one of ordinary skill in the art would have recognized regions of IL- 21 polypeptide that should not be mutated in an IL-21 variant". In addition, Applicants argue that "assays to determine suitable IL-21 variants are described in the specification or known in the art. For example, the claims require that the IL-21 variant produces the same physiological effect

produced by binding of the IL-21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20), induces expression of mRNA for Blimp-1 and Bcl-6 (see, e.g., page 53, lines 27-29), and inhibits expression of Pax5 mRNA (see, e.g., page 53, lines 27-30). Assays to determine if an IL-21 variant produces the above-described effects (e.g., real-time PCR) are known in the art and are described in the specification at, for instance, page 41, line 19, through page 44, line 16; and Examples 3-5. Accordingly, based on the teachings in the specification and what was known in the art, one of ordinary skill in the art would have recognized how to perform the inventive methods without undue experimentation and with an expectation of success". Such is not persuasive.

The examiner refers Applicants to the reasons of record and the reasons set forth in the paragraphs above. In addition the mere contemplation of how to make the claimed genus of nucleic acids in the specification at page 31, lines 1-20, is not sufficient to support the present claimed invention directed to a genus of IL-21, a genus of IL-21 variants and a genus of unidentified fragments of SEQ ID No. 1 that differ from SEQ ID No. 1 by 1-5 amino acids retaining full or even partial activity. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence it would require undue experimentation to determine alternative amino acid sequences other than amino acid sequence of SEQ ID No. 1 meeting the claim requirements to enhance an immune response in a subject or to treat a subject with a condition comprising a specific deficiency of at least one of memory B and plasma cells.

Conclusion

Claims 5, 8, 10-12, 18, 20 and 32-35 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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